UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/816,081	04/01/2004	David B. Rozema	Mirus.035.02.1	8619

25032 7590 02/03/2009

MIRUS CORPORATION
505 SOUTH ROSA RD
MADISON, WI 53719

EXAMINER	
DUNSTON, JENNIFER ANN	
ART UNIT	PAPER NUMBER
1636	
MAIL DATE	DELIVERY MODE
02/03/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/816,081	ROZEMA ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19,22,23 and 27-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19,22,23 and 27-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 April 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/31/2008 has been entered.

Receipt is acknowledged of an amendment, filed 10/31/2008, in which claim 19 was amended. Claims 19, 22, 23 and 27-32 are pending.

Election/Restrictions

Applicant elected Group II without traverse in the reply filed on 9/18/2006. Currently, claims 19, 22, 23 and 27-32 are under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 32 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 32 recites the limitation "said complex" in line 1. Claim 32 depends from claim 19, which recites a "binary complex" and a "ternary complex." Thus, it is unclear if claim 32 is referring to the binary complex or the ternary complex.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 19, 23 and 27-29 are rejected under 35 U.S.C. 102(b) as being anticipated by Wolff (WO 00/75164 A1, cited in a prior action; see the entire reference). This is a new rejection.

Regarding claim 19, Wolff teaches a method for delivering a polynucleotide to the cytoplasm of a cell, comprising (i) condensing the polynucleotide with a poly-L-lysine (PLL) polycation to form a binary complex; (ii) associating the binary complex with a reversibly inhibited membrane active polymer to form a ternary complex (recharging); and (iii) delivering the ternary complex to a cell, wherein the ternary complex is endocytosed by the cell (e.g., page 76, line 15 to page 78, line 15; page 106, line 19 to page 107, line 15). Wolff teaches the method where the "reversibly inhibited membrane active polymer" is a membrane active polyamine selected from the group consisting of melittin, KL_3, KL_3PLL to which a plurality of disubstituted

maleic anhydride derivatives are reversibly linked via pH labile bonds (e.g., paragraph bridging pages 52-53; page 76, line 15 to page 78, line 15). Further, Wolff teaches that linkage of the disubstituted maleic anhydride derivatives to the membrane polyamine polymer inhibits liposome leakage activity (as measured by red blood cell lysis) of the membrane active polyamine and cleavage of the disubstituted maleic anhydride derivatives from the reversibly inhibited membrane active polymer restores liposome leakage activity of the membrane active polyamine (e.g., paragraph bridging pages 21-22; page 24, line 5 to page 25, line 4; paragraph bridging pages 52-53; page 103, line 25 to page 104, line 12).

Regarding claim 23, Wolff teaches the method where the membrane active polyamine disrupts an endocytic membrane after cleavage of the disubstituted maleic anhydride moiety thereby providing delivery of the polynucleotide to the cytoplasm of the cell (e.g., paragraph bridging pages 52-53; page 76, line 15 to page 78, line 15; page 106, line 19 to page 107, line 15).

Regarding claim 27, Wolff teaches the method where the disubstituted maleic anhydride derivatives are derived from reaction of the membrane active polymer with carboxydimethylmaleic anhydride (2-propionic-3-methylmaleic anhydride (e.g., paragraph and bridging pages 52-53; page 64, lines 1-18; page 66, lines 22-27; page 77, line 22 to page 78, line -15).

Regarding claim 28, Wolff teaches the method where the disubstituted maleic anhydride derivatives are cleaved from the polyamine in an endosome (e.g., paragraph bridging pages 52-53; page 76, line 15 to page 78, line 15; page 106, line 19 to page 107, line 15).

Regarding claim 29, Wolff teaches the method where the membrane active polymer is KL_3-PLL, for example, which has a molecular weight greater than 10,000 Daltons (e.g., page 65, lines 15-27).

Claims 19, 23 and 27-29 are rejected under 35 U.S.C. 102(e) as being anticipated by Rozema et al (US Patent Application Publication 2004/0156909 A1; see the entire reference). This is a new rejection.

The applied reference has a common inventor and assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Regarding claim 19, Rozema et al teach a method for delivering a polynucleotide to the cytoplasm of a cell, comprising (i) condensing the polynucleotide with a polyvinylether polycation to form a binary complex; (ii) associating the binary complex with a negatively charged reversibly inhibited membrane active polymer, which is a CDM-modified polyvinylether polyamine polymer to form a ternary complex; and (iii) delivering the ternary complex to a cell, wherein the ternary complex is endocytosed (e.g., paragraphs [0008] and [0059]; Tables 1 and 4). Rozema et al teach that sufficient hydrophobicity incorporated into the polyvinylether gives the polymer membrane activity (e.g., paragraph [0031]). Modification by reaction with CDM can inhibit its membrane activity, and incubation of the modified polymer in

the endosome at acidic pH restores membrane activity (e.g., paragraph [0031]). CDM is a disubstituted maleic anhydride derivative (carboxylate-substituted dimethylmaleic anhydride, e.g., paragraph [0030]).

Regarding claim 23, Rozema et al teach the method where the membrane active polyamine disrupts an endocytic membrane thereby providing delivery of the polynucleotide into the cytoplasm of the cell (e.g., paragraphs [0031] and [0059]; Table 4).

Regarding claim 27, Rozema et al teach the method where the disubstituted maleic anhydride derivative is carboxydimethylmaleic anhydride (CDM, e.g., paragraphs [0030] and [0059]).

Regarding claim 28, Rozema et al teach the method where the inhibitors are cleaved from the polyamine in the endosome (e.g., paragraphs [0031] and [0059]).

Regarding claim 29, where the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of the claimed product. See *In re Ludtke* 441 F.2d 660, 169 USPQ 563 (CCPA 1971). Whether the rejection is based on "inherency" under 35 U.S.C. 102, or "prima facie obviousness" under 35 U.S.C. 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. *In re Best, Bolton, and Shaw*, 195 USPQ 430, 433 (CCPA 1977) citing *In re Brown*, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972). In the instant case, the polyamine polymers of Rozema et al are produced by a substantially identical

process (Rozema et al, paragraph [0051] and specification pages 16-17, Example 2) and would be expected to produce polyamines with a molecular weight of at least 10,000 Daltons.

Claims 19, 23, 27 and 28 are rejected under 35 U.S.C. 102(e) as being anticipated by Lewis et al (US Patent Application Publication No. 2003/0224055 A1; see the entire reference). This is a new rejection.

The applied reference has a common inventor and assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Regarding claim 19, Lewis et al teach a method for delivering a polynucleotide to the cytoplasm of a cell, comprising (i) condensing the polynucleotide with polymer 220, a polyvinylether based polyamine that is a polycation, to form a binary complex; (ii) associating the binary complex with a negatively charged reversibly inhibited membrane active polymer, which is polymer 220 modified with 2-propionic-3-methylmaleic anhydride (carboxy dimethylmaleic anhydride or CDM) to form a ternary complex; and (iii) delivering the ternary complex to the cell, wherein the ternary complex is endocytosed (e.g., paragraphs [0059], [0070] and [0071]; Table 2; Figures 1D and 3). Lewis et al teach that butyl groups, such as those found in polymer 220, are able to disrupt membranes (e.g., paragraph [0045]; Figure 1D). Acylation of

these polyvinylethers with a disubstituted maleic anhydride, such as CDM, inhibits membrane activity, which is restored by acidification that occurs in the endosome (e.g., paragraph [0045]).

Regarding claim 23, Lewis et al teach the method where the membrane active polyamine disrupts an endocytic membrane thereby providing the delivery of the polynucleotide to the cytoplasm of the cell (e.g., paragraphs [0045], [0059], [0070], [0071]; Table 2; Figures 1D and 3).

Regarding claim 27, Lewis et al teach the method where the disubstituted maleic anhydride derivative is carboxydimethylmaleic anhydride (e.g., paragraph [0070]).

Regarding claim 28, Lewis et al teach that the CDM inhibitors are cleaved from the 220 polymer in the endosome (e.g., paragraph [0045]).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 22 and 30-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wolff (WO 00/75164 A1, cited in a prior action; see the entire reference in view of Wolff (WO 00/03694 A1, cited in a prior action; see the entire reference). This is a new rejection.

Claim 32 is interpreted as limiting the ternary complex to on that has a net negative charge.

The teachings of Wolff (WO 00/75164 A1) are described above and applied as before. Wolff teaches that DNA/polycation complexes can be recharged with a polyanion and crosslinked (e.g., page 13, lines 15-17; page 36, lines 9-17). Wolff teaches that particle formation should be reversible to allow escape of DNA from the endosome, and conditions that cause the reverse of particle formation may be the pH (e.g., page 10, lines 22-29). Wolff teaches the use of pH-labile bonds to allow reversal under lower pH conditions of the endosome (e.g., page 19, lines 25-30; page 22, line 32 to page 23, line 25; page 37, lines 1-14). Wolff teaches that disulfide bonds are inherently labile and can be used to construct very pH-labile bonds (e.g., page 48, lines 23-26). Further, Wolff teaches that it is preferable to use DNA complexes of about 100 nm (e.g., page 8, lines 5-17). Moreover, Wolff teaches that PEG chains act as a steric stabilizer that prevents aggregation of final polymer by sterically hindering particle to particle electrostatic interactions (e.g., page 44, lines 9-14). Wolff teaches the covalent attachment of PEG to 2-propionic-3-methylmaleic anhydride (carboxydimethylmaleic anhydride, CDM) (e.g., page 66, lines 10-20), and the reaction of CDM-PEG with PLL (e.g., page 107, lines 26-29).

Wolff (WO 00/75164 A1) do not specifically teach the method where the polycation is crosslinked to the reversibly inhibited membrane active polymer via a pH-labile bond to form a negatively charged, salt stable nanoparticle.

Wolff (WO 00/03694 A1) teaches the formation of condensed DNA with a polycation to form a binary complex, which is recharged with a polyanion (e.g., paragraph bridging pages 17-18). Wolff teaches that the binary complex of DNA and polycation can be recharged with a polyanion to provide the ternary complex with a net negative charge (e.g., paragraph bridging pages 17-18). Further, Wolff teaches that the interaction between the polycation and polyanion of the ternary complex may be via a covalent crosslink between cationic and anionic sites, including cleavable crosslinking systems, including those containing disulfide bonds (e.g., paragraph bridging pages 17-18). With regard to particle size of ternary complexes, Wolff teaches that a DNA/PLL binary complex recharged with succinic anhydride has a net negative charge and forms nanoparticles (e.g., page 18, lines 9-16; page 27, line 3 to page 28, line 8). When the cationic and anionic layers of the DNA particles were crosslinked, the stability of the nanoparticles was substantially improved (e.g., page 27, lines 9-11; Table 2). Furthermore, binary complexes of DNA and PLL recharged with PEG-SPLL displayed higher stability as compared to non-pegylated particles (e.g., page 28, lines 10-25; Table 3).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of delivering a polynucleotide to the cytoplasm of a cell of Wolff (WO 00/75164 A1) to include the cross-linking of the polycation of the binary complex with the polyanion used to recharge the binary complex and form a ternary complex as taught by Wolff (WO 00/03694 A1) because Wolff (WO 00/75164 A1) teach it is within the ordinary skill

in the art to use a recharging process to form a ternary complex and Wolff (WO 00/03694 A1) teach covalent linking of the polyanion used to recharge the binary complex containing the polycation. Furthermore, Wolf (WO 00/03694 A1) teaches the use of labile linkages in the crosslink, such as those containing a disulfide bond, and Wolff (WO 00/75164 A1) teaches very pH-labile bonds comprising a disulfide bond. Moreover, both Wolff references teach the addition of PEG to stabilize the complex, and Wolff (WO 00/03694 A1) teaches that pegylation stabilizes the particle while maintaining a small nanoparticle of about 100 nm, and Wolff (WO 00/75164 A1) teaches that particles of about that size are desirable.

One would have been motivated to make such a modification in order to receive the expected benefit of providing a more stable nanoparticle as taught by Wolff (WO 00/03694 A1), which is capable of dissociating in the endosome to deliver the polynucleotide as taught by Wolff (WO 00/75164 A1). Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Response to Arguments - 35 USC § 103

The rejection of claims 19, 22, 23 and 29-32 under 35 U.S.C. 103(a) as being unpatentable over Wolff (WO 00/03694 A1) in view of Richardson et al has been withdrawn in view of Applicant's amendment to the claims in the reply filed 10/31/2008.

Applicant's arguments with respect to claims 27 and 28 under 35 U.S.C. 103(a) as being unpatentable over Wolff (WO 00/03694 A1) in view of Richardson et al and further in view of Wolff (WO 00/75164 A1) have been considered but are moot in view of the new ground(s) of

rejection presented above. Wolff (WO 00/75164 A1) teaches linkage of disubstituted maleic anhydride derivatives reversibly linked via pH labile bonds to a polyamine, where linkage of the disubstituted maleic anhydride derivatives to the polymer inhibit liposome leakage activity of the polyamine and cleavage of the disubstituted maleic anhydride derivatives from the polyamine restores liposome leakage activity.

The rejection of claims 19, 22, 23 and 30-32 under 35 U.S.C. 103(a) as being unpatentable over Wolff (WO 00/03694 A1) in view of Rittner et al has been withdrawn in view of Applicant's amendment to the claims in the reply filed 10/31/2008.

Applicant's arguments with respect to claims 27 and 28 under 35 U.S.C. 103(a) as being unpatentable over Wolff (WO 00/03694 A1) in view of Rittner et al and further in view of Wolff (WO 00/75164 A1) have been considered but are moot in view of the new ground(s) of rejection presented above. Wolff (WO 00/75164 A1) teaches linkage of disubstituted maleic anhydride derivatives reversibly linked via pH labile bonds to a polyamine, where linkage of the disubstituted maleic anhydride derivatives to the polymer inhibit liposome leakage activity of the polyamine and cleavage of the disubstituted maleic anhydride derivatives from the polyamine restores liposome leakage activity.

Response to Amendment

The declaration under 37 CFR 1.132 filed 10/31/2008 is sufficient to overcome the rejection of claims 19, 22, 23 and 29-32 based upon the application of the Wolff (WO 00/03694 A1) reference under 35 USC 103(a). Wolff (WO 00/03694 A1) does not teach the absence of liposome leakage activity upon linkage of disubstituted maleic anhydride derivatives to a

polyamine membrane active polymer and restoration of the activity upon the cleavage of the disubstituted maleic anhydride derivatives.

The declaration under 37 CFR 1.132 filed 10/31/2008 is insufficient to overcome the rejection of claims 27 and 28 based upon the Wolff (WO 00/75164 A1) reference as set forth in the last Office action because: Wolff (WO 00/75164 A1) teaches the absence of liposome leakage activity upon linkage of disubstituted maleic anhydride derivatives to a polyamine membrane active polymer and restoration of the activity upon the cleavage of the disubstituted maleic anhydride derivatives. It is noted that the rejection of claims 27 and 28 under 35 USC 103(a) are moot in view of the new rejections of claims 27 and 28 based upon the Wolff (WO 00/75164 A1 reference) under 35 USC 102(b).

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached at 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jennifer Dunston, Ph.D.
Examiner
Art Unit 1636

/JD/

/Celine X Qian /

Primary Examiner, Art Unit 1636